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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,054	11/20/2003	Stephen N. Jones	07917-178001 / UMMC 03-14	3347

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FISH & RICHARDSON PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
SGAGIAS, MAGDALENE K	
ART UNIT	**PAPER NUMBER**
1632	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/719,054	JONES ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26,28,29 and 31-36* is/are pending in the application.

4a) Of the above claim(s) *1-22 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-26,28,29 and 32-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/4/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/4/07 has been entered.

Applicant's arguments filed 4/4/07 have been fully considered but they are not persuasive. Claim amendments have been entered. Claims 1-26, 28-29, 31-36 are pending. Claims 1-22 and 31 are withdrawn. Claims 27 and 30 are canceled. Claims 23-26, 28-29 and 32-36 are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23-26, 28-29 and 32-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method of treating a subject having, a wingless-related MMTV integration site 5a (Wnt5a)-associated leukemia or non-Hodgkin's lymphoma by administering to the subject a blood cell transduced with a nucleic acid encoding Wnt5a, wherein the amount of nucleic acid molecule delivered is sufficient to generate therapeutically

effective amount of Wnt5a. Embodiments limit the method to administering a blood cell by removing a blood cell from a subject, transducing the blood cell with Wnt5a, optionally culturing the cell and returning the cell to the subject. Embodiments further limit the blood cell to a hematopoietic stem cell and further limitations to a blood lymphoid cell.

The specification teaches Wnt5a heterozygous mice develop B cell lymphomas and chronic myeloid leukemia with loss of heterozygosity for Wnt5a function (example 9). The specification teaches Wnt5a functions as a tumor suppressor gene in mice and Wn5a+/- mice develop B cell lymphomas (specification p 42, example 1). The specification teaches Ragl-/- mice, which lack the ability to produce B- and T-cell lymphocytes received irradiation before cell transfer of 5 X 10^6 wild type or Wnt5a null fetal liver cells prepared from El6 fetal liver by intravenous injection into the lethally irradiated Ragl-/- mice. Both the percentage and the absolute numbers of pro-B, pre-B, IgM+ B cells in bone marrow, and mature follicular B cells in the spleen were greater in mice transplanted with Wnt5a-null fetal liver cells than those rescued with wild type fetal liver cells (FIG. 17A-F; FIG. 18). The specification teaches Wnt5a signals the Wnt5a/Ca++ pathway to modulate B cell proliferation in the fetal liver cells isolated from Wnt5a-null mice (specification p 45, example 3). The specification teaches that Wnt5a signals through the non-canonical wnt5a/Ca++ pathway and downregulates cyclin D1 activity in mouse Wnt5a-null fetal liver cells in vitro (specification p 47-48, example 6). However, the specification has failed to correlate the in vitro downregulation of cyclin D1 in Wnt5a-null fetal liver cells to the administration of a blood cell transduced with Wnt5a to a subject, wherein a therapeutically effective amount of Wnt5a is produced resulting in the treatment of leukemia or non-Hodgkin's lymphoma as required in the instant invention. Moreover the specification has failed to correlate the administration of the wild type or Wnt5a null fetal liver cells prepared from El6 fetal liver by intravenous injection into the lethally irradiated Ragl-/- mice to the administration of a blood cell

transduced with Wnt5a to a subject by way of the claimed methods resulting in the treatment of Wnt5-associated leukemia or non-Hodgkin's lymphoma. Thus, as enablement requires the specification to teach how to make and use the claimed invention, the specification fails to enable the claimed methods for treating leukemia or non-Hodgkin's lymphoma. It would have required undue experimentation to make and use the claimed invention without a reasonable expectation of success.

At the time of filing the art taught that cell based gene therapy was unpredictable without undue experimentation. With regard to blood cell based gene therapy, while progress has been made in recent years for blood cell transfer transduced with different genes in vivo, expansion of hematopoietic stem cells (HSCs), homing to desired tissues, and expression of therapeutic amounts of the transgene continues to be a problem. For example, **Sorrentino** (Nature, 4: 878-888, 2004) while reviewing the strategy for amplifying HSCs based on the wnt-signaling pathway including the wnt5a concludes that further research is required to determine which specific WNT molecules are best suited to inducing the expansion of HSCs (p 883, 2nd column, 3rd paragraph). Sorrentino reports for controlling the expansion of HSCs there is evidence that modulating the expression of wnt-family genes can be used to achieve expansion of mouse HSCs (p 879, 1st column, last paragraph). However, there is less information regarding the expansion of human HSCs, in part because HSC assay systems are not as well defined for human HSCs as for mouse HSCs (Sorrentino, p 879, bridge 1st to 2nd column). Sorentino reports that investigators have used immunodeficient NOD–SCID mice (that is, mice on a non-obese diabetic and severe combined immunodeficient background) to study engraftment with human haematopoietic cells; however, haematopoietic progenitors, rather than HSCs, dominate the early phase of engraftment (p 879, 2nd column). Another problem with the NOD–SCID model is the absence of human T-cell development (p 879, 2nd column). Sorerntino concludes

that eventually, it will be important to validate approaches for HSC expansion in non-human primate systems and, ultimately, in humans (p 879, 2nd column).

Homing of transduced blood cells in vivo is unpredictable as has been taught by the art. The art teaches that downregulation of beta1 integrin on primitive hematopoietic cells during ex vivo expansion reduces their homing efficiency and negatively impacts hematopoietic reconstitution in vivo (**Szilvassy et al,** Experimental Hematology, 29: 1494-1502, 2001) (abstract). Szilvassy for example, reports that the dowregulation of beta 1 integrin in hematopoietic stem cells (HSCs) during their expansion in vitro has important implications for cell therapies using cultured hematopoietic cells because it demonstrates directly that clonal in vitro assays are largely irrelevant to predicting in vivo engraftment potential in situations where expansion is accompanied by loss of integrin expression (p 1500, 2nd column, last paragraph). Szilvasky suggest that the disappointing repopulating activity of expanded murine and human hematopoietic cells observed by many investigators is, at least in part, related to loss of integrin expression on otherwise functionally intact cells (p 1500, 2nd column last paragraph). Others have observed similar downregulation of other adhesion molecules on hematopoietic cells following cytokine-stimulated proliferation in vitro (Szilvassy, p 1500 bridge 15001).

The working examples do not provide guidance for the in vivo administration of a blood cell transduced with wnt5a, wherein a therapeutically effective amount of wnt5a is produced for treating leukemia or non-Hodgkin's lymphoma. The administration of mouse Wnt5a null fetal liver cells into the lethally irradiated Ragl-/- mice which resulted in an increase of the numbers of B cells in the bone marrow and the spleen of mice compared to wild type fetal liver cells is not correlatable to treating wnt5a-associated leukemia or non-Hodgkin's lymphoma with a wnt5a transduced blood cell. The administration of wnt5a-null fetal liver cells does not provide guidance to overcome the limitations of expansion, and homing of transduced wnt5a HSCs as

cited by the art of record. Moreover the downregulation of cyclin D1 by wnt5a in mouse Wnt5a-null fetal liver cells in vitro does not provide guidance for the treating leukemia or non-Hodgkin's lymphoma by way of the claimed methods in vivo. This is because the in vitro data are not correlatable to the in vivo microenvironment where the transduced blood cell has to pass through the complex organization of tissues and organs unlike the in vitro culture microenvironment. The in vivo microenvironment is not correlatable to the in vitro microenvironment with regard to growth factors that will regulate cyclin D1 downregulation by wnt5a in the wnt5a-transduced blood cell as compared to wnt5a-null cell in vitro. The in vitro data cannot be extrapolated to the in vivo data because it is unpredictable as to whether the wnt5a produced by the tranduced wnt5a blood cells is produced at a therapeutic level to rescue the wnt5a-negative cells in vivo.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the treatment of a Wnt5a-associated leukemia or non-Hodgkin's lymphoma, the lack of guidance provided by the specification for the treatment of a Wnt5a-associated leukemia or non-Hodgkin's lymphoma, the absence of working examples that correlate to the treatment of a Wnt5a-associated leukemia or non-Hodgkin's lymphoma, the unpredictable state of the art with respect to blood cell-based Wnt5a gene therapy, the undeveloped state of the art for the treatment of a Wnt5a-associated leukemia or non-Hodgkin's lymphoma, and the breadth of the claims directed to all types of Wnt5a-associated leukemias, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Applicants argue Per MPEP 2164.02, an applicant need not have actually reduced the invention to practice prior to filing. The Federal Circuit has blessed reliance on in vitro data in Cross v. Iizuka, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985):

> ... "[B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed in vitro utility and an in vivo activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence."

In this case, the desired "pharmacological activity" is a decrease in cellular proliferation in cells that have lost Wnt5a, to treat leukemia or non-Hodgkin's lymphoma. The in vitro examples presented in the specification demonstrate that expressing Wnt5a in these cells reduces proliferation. Thus, there is a direct correlation between the disclosed in vitro utility and in vivo activity.

These arguments are not persuasive because Cross v. Iizuka relates to utility under 35 USC 101, whereas the present rejection is under enablement how to use the claimed invention under 35 USC 112 first paragraph. Applicants claimed invention has no utility, and isn't enabled for reasons of record and for reasons as set forth above. In vivo gene therapy, as presently claimed requires testing of parameters not existing in the in vitro system disclosed by the Applicants. Delivery of the vector to an intact body is materially different and unpredictable. The specification fails to provide routes of delivery of vectors that would provide a treatment effect. Further it is noted the claims do not require a particular therapeutic amount Wnt5a produced resulting in the treatment of leukemia or non-Hodgkin's lymphoma.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter

Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Magdalene K. Sgagias, Ph.D.
Art Unit 1632

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP 1800/1630